SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

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Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2004D-0377 International Conference on Harmonisation; Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Dear Sir/Madam

Schering-Plough has reviewed the above referenced Draft Guidance, and we offer the following comments for your consideration.

During the last several years, the major pharmaceutical companies have instituted extensive preclinical screening of new chemical entities (NCEs) for potential interactions with the HERG K-channel starting in the early discovery screening. This screening, and other assessments, have been used as criteria in the hit-to-lead optimization process. As a result, NCEs now entering preclinical development should have a far lower arrhythmic potential. In parallel to instituting measures to reduce the arrhythmogenic potential of NCEs emerging from discovery, preclinical safety studies evaluating the NCE interacting with cardiac channels have expanded significantly. Those NCEs having properties associated with cardiac arrhythmia risk are being removed from development. Overall, the additional precautions for drug lead to qualification for initial human use have reduced the likelihood of arrhythmia.

The ICH S7B should serve a significant role in the design of the clinical pharmacology study and in interpretation of the results. Ideally the rigor of a clinical pharmacology study would be tailored by the absence or presence of a signal in robust S7B studies.

2004D-0377 C14

Comments on ICH E14

Section 2.1 Design Considerations

Line 159 "...would be needed in almost all cases for regions... For regions where non-clinical data ..." needs to be revised based on a harmonized position of the EWG. The EWG needs to reconcile regional differences in the role that S7B serves in designing and interpreting the data from E14 studies.

Section 2.1.2 The 'Thorough QT/QTc study': Dose Effect and Time Course Relationships

Given biological variability and the prospect of inclusion of individuals with silent Long QT Syndrome, absent an overt phenotype or other undetected risk factor, it may not be advisable to recommend inclusion of a positive control agent that could put normal volunteers at risk of proarrhythmia. The experience to date may suggest that this risk is manageable, however, with the adoption of the E14 guideline, the population exposed to this protocol will significantly increase. This concern should be considered when making such a recommendation in the guidelines.

Lines 214-216. The use of drug inhibitors to increase plasma concentration of the NCE raises several concerns. Many of the protocol cytochrome inhibitors were developed several years ago and have not been extensively studied with respect to their cardiovascular properties – representing potential confounders to interpreting study results. Among the inhibitors commonly recommended there are several which have inherent safety and tolerability constraints. While these constraints create only minor limitations during their use as prototype inhibitors in evaluating drug interactions, the use of these compounds in cardiac pharmacodynamic studies has only been explored on a limited basis. Clinical observations of some prototype inhibitor drugs have raised questions about their cardiac effects.

The majority of drugs will have their greatest cardiac effects at C_{max} or just post C_{max}. To achieve greatest concentrations, higher monotherapy doses are most likely to achieve this goal. Drugs that inhibit metabolism or excretion are more likely to increase drug exposure (AUC) while having lesser effects on C_{max}. For most drugs high dose monotherapy would be the best approach as stated in the guidance. For those compounds in which AUC of the drug can be associated with cardiac pharmacodynamic changes, the use of inhibitors of metabolism may be of use when exposure is limited by absorption or tolerability at peak concentrations. For the majority of drugs more than one pathway for clearance exists. Two or more metabolic pathways would have to be inhibited to achieve significant increases in C_{max} and to lesser extent AUC. The use, of multiple inhibitors to achieve maximum peak concentrations and exposures is likely to further complicate the interpretation of pharmacodynamic parameters. Overall the use of metabolic inhibitors should be avoided in a "thorough QT/QTc study" for both subject safety and subsequent interpretation of the results.

Section 2.1.3 Clinical Trial Evaluation After the 'Thorough QT/QTc Study'

Line 314. This statement should be clarified to indicate that testing in these populations (lines 317-322) would be appropriate if the intention is not to restrict treatment of one or more of the subgroups with the test substance. Otherwise, if any of the subgroups are restricted from exposure to the test substance due to a cause for concern, further study in these individuals may not be justified.

Section 5.1 Relevance of QT/QTc Interval Prolonging Effects to the Approval Process

Line 625. "Failure to perform an adequate non-clinical and clinical assessment...can likewise be justification to delay or deny marketing authorization." The EWG should be clear on the importance of S7B data in reference to defining the protocol and interpretation of the study outcome of E14 studies. If the importance of S7B is retained in E14, then the statement in Section 5.1 appears to be valid. IF the consensus of the EWG is that S7B does not serve as an important role in E14, then reference to non-clinical studies should be removed.

Schering-Plough thanks you for the opportunity to present our comments on this draft guidance.

Sincerely,

Ronald Garutti, MD
Group Vice President
Global Regulatory Affairs

RG/am

cc: Jim Macleod
Alan Bass
Gretchen Trout